

Published in final edited form as:

Transplantation. 2015 May; 99(5): 1051–1057. doi:10.1097/TP.0000000000000449.

Association of Antibody Induction Immunosuppression with Cancer After Kidney Transplantation¹

Erin C Hall, MD MPH^{2,3}, Eric A Engels, MD MPH³, Ruth M Pfeiffer, PhD³, and Dorry L Segev, MD PhD^{2,4}

²Department of Surgery, Johns Hopkins School of Medicine, 720 Rutland Ave, Baltimore MD 21205

³Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Dr, Bethesda, MD 20892

⁴Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore MD 21205

Abstract

Background—Induction immunosuppression is a mainstay of rejection prevention after transplantation. Studies have suggested a connection between antibody induction agents and cancer development, potentially limiting important immunosuppression protocols.

Methods—We used a linkage of U.S. transplantation data and cancer registries to explore the relationship between induction and cancer after transplantation. 111,857 kidney recipients (1987–2009) in the Transplant Cancer Match Study, which links the Scientific Registry for Transplant Recipients and U.S. cancer registries, were included. Poisson regression models were used to estimate adjusted incidence rate ratios (aIRR) of non-Hodgkin lymphoma (NHL)and other cancers with increased incidence after transplantation (lung, colorectal, kidney, and thyroid cancers, plus melanoma).

Results—2,763 cancers of interest were identified. Muromonab-CD3 was associated with increased NHL (aIRR=1.37, 95% CI 1.06–1.76). Alemtuzumab was associated with increased NHL (aIRR=1.79, 95% CI 1.02-1-3.14), colorectal cancer (aIRR=2.46, 95% CI 1.03–5.91), and thyroid cancer (aIRR=3.37, 95% CI 1.55–7.33). Polyclonal induction was associated with increased melanoma (aIRR=1.50, 95% CI 1.06–2.14).

¹Erin Hall made substantial contributions to the study conception and design, data analysis and interpretation, drafting of the article, and had final approval of the manuscript. Eric Engels made substantial contributions to study conception and design, data analysis and interpretation, made critical revisions, and had final approval. Ruth Pfeiffer made substantial contributions to the study design, data analysis, made critical revisions, and had final approval of the manuscript. Dorry Segev made substantial contributions to the study conception and design, data analysis and interpretation, made critical revisions, and had final approval of the manuscript. Sources of support: Intramural Research Program (National Cancer Institute): EAE and RMP; National Institute of Health training grant: ECH; Sanofi Pharmaceuticals (Investigator-Initiated Grant): DLS.

Address for Correspondence: Dorry Segev, M.D. Ph.D., Director of Clinical Research, Transplant Surgery, Johns Hopkins Medical Institutions, 720 Rutland Ave, Ross 771B, Baltimore, MD 21205, 410-502-6115 (tel) 410-614-2079 (fax), dorry@jhmi.edu. Conflict of interest: Dorry Segev receives consulting honoraria from Pfizer, Astellas, and Sanofi. He also received an investigator-initiated grant from Sanofi Pharmaceuticals. Sanofi pharmaceuticals now owns Genzyme, manufacturer of thymoglobulin and alemtuzumab. At no time did Sanofi pharmaceuticals or any personnel from Sanofi pharmaceuticals have access to the data or contribute to data analysis. None of the other authors have any conflicts of interest to report.

Conclusions—Our findings highlight the relative safety with regard to cancer risk of the most common induction therapies, the need for surveillance of patients treated with alemtuzumab, and the possible role for increased melanoma screening for those patients treated with polyclonal anti-T cell induction.

Keywords

immunosuppression and cancer risk; cancer after transplantation; alemtuzumab risk

Introduction

Cancer is the third most common cause of death after kidney transplantation. (1) When compared to the general population, transplant recipients have increased risk for dozens of malignancies (2,3) and have higher mortality rates due to cancer when compared to the general population. (4) The immunosuppression that transplant recipients must receive in order to prevent rejection is thought to increase cancer risk through decreased control of oncogenic viral infections and immunosurveillance similarly to other immunosuppressed populations. (3) Antibody induction agents are a potent group of immunosuppressive therapies that reduce the risk of rejection primarily through T-cell depletion or modulation; these agents are a mainstay of acute rejection prevention for many kidney transplant recipients. (5,6) Use of induction immunosuppression and the agent chosen are potentially modifiable risk factors for cancer after transplantation, however the associations between antibody immunomodulation and cancer after transplantation remain poorly understood.

Some studies have suggested an association between antibody induction and cancer after transplantation, (7–11) while others have failed to demonstrate this association. (12–15) These conflicting results may be due to differences in categorization of induction agents, the time period covered, and cancer outcomes of interest. Small sample sizes have forced researchers to group together different antibody induction agents and cancer outcomes. These heterogeneous exposures and outcomes make it difficult to gain mechanistic understanding of the role of induction immunosuppression and cancer risk, and offer little guidance to clinicians. Furthermore, antibody induction agents with novel mechanisms, such as alemtuzumab, remain mostly uninvestigated in terms of cancer risk after transplantation. The few studies that do exist have similar limitations to other studies of induction and cancer risk: only post-transplant lymphoproliferative disorder (PTLD) has been examined, inferences are limited by relatively short follow-up time, and results have been contradictory. (11,16)

One way to address this sample size problem is to use the data collected by the US-wide Organ Procurement and Transplantation Network (OPTN) and contained in the Scientific Registry of Transplant Recipients (SRTR). While capture of recipient, donor, transplant, and in-hospital immunosuppression data are excellent in this database, a reliance on transplant center reporting of cancer outcomes causes known limitations in cancer ascertainment. (17) Previous studies using OPTN data to explore cancer risk associated with antibody induction have, because of the nature of limited cancer ascertainment in the registry, censored follow-up at three years post-transplant and limited the outcome of interest to early PTLD,

curtailing the potential power of this registry and still producing conflicting inferences. (10,11,14,15)

To improve inferences about the association between specific antibody induction agents and cancers after kidney transplantation, we used the recent, population-based Transplant Cancer Match (TCM) Study. Unlike previous U.S.-based studies, the TCM Study takes advantage of mandatory cancer reporting to state and regional cancer registries, capturing cancers in transplant recipients that occur after the transplant center loses follow-up. Using the TCM data, we tested our hypothesis that antibody induction immunosuppression is most associated with those cancers that are known to be virus-related, including non-Hodgkin lymphoma (NHL). We were also able to investigate the association between antibody induction immunosuppression and common non-virus-related cancers including lung cancer, kidney cancer, colorectal cancer, thyroid cancer, and melanoma (among non-Hispanic white recipients). The size of this study allowed for categorization of antibody induction exposures and cancer outcomes that are clinically and mechanistically relevant. The availability of high quality data over 20 years allowed us to take into account changes in antibody induction use over time. Our results could help guide clinician decision making with regard to risks and benefits of antibody induction and the need for screening in kidney recipients who received induction immunosuppression. In addition, characterization of the risk of specific cancers associated with mechanistically relevant categorization of induction immunosuppression may provide new insights into cancer development.

Results

Study Population

Cancer registry linkage was available for 111,857 kidney recipients who met inclusion criteria, with a median follow-up of 3.5 years (range: 1 day to 21.7 years, IQR: 1.4–6.5 years). Approximately half of kidney recipients (53.6%) were treated with an antibody induction agent. Demographics of those receiving each induction agent varied only slightly (Table 1). Of those receiving polyclonal antibodies, a higher percentage were of black race (26.2%) or undergoing retransplantation (14.2%). A higher percentage of those receiving muromonab-CD3 were 18–35 years old (25.7%) and a lower percentage had zero HLA mismatches (9.1%) or received kidneys from living donors (16.3%) compared to other induction agents.

Temporal Trends in Induction

Use of antibody induction, as well as the agents used, changed over time (Figure 1). Among induction agents used, the proportion of recipients receiving polyclonal anti-T cell agents increased from 22.6% to 66.4%. Likewise, anti-IL2R usage increased since its introduction in 1995 from 0.4% to 22.4%. The peak use of muromonab-CD3 occurred in the early 1990s with rapidly decreasing proportion of recipients receiving this agent after 1999. Alemtuzumab was introduced in 2000 and its use remains relatively uncommon (6.9% of recipients between 2002 and 2009).

Polyclonal Anti-T Cell

Associations with induction agents are shown for virus-related cancers (Table 2) and other cancers (Table 3). Polyclonal anti-T cell induction was not associated with NHL (aIRR=0.96, 95% CI 0.77–1.20, p=0.7 and), non-NHL VRCs (aIRR=1.11, 95% CI 0.82–1.53, p=0.5 and), or all VRCs (aIRR=1.01, 95% CI 0.84–1.21, p=0.9). Polyclonal anti-T cell induction was associated with increased melanoma among non-Hispanic whites (aIRR=1.50, 95% CI 1.06–2.14, p=0.02); when restricted to transplant recipients between 2000 and 2009, this association was of similar magnitude but no longer statistically significant (aIRR 1.52, 95% CI 0.85–2.69, p=0.2). Similarly, when restricted to those patients who received rabbit anti-thymocyte globulin, the association persisted, but was no longer statistically significant (aIRR 1.65, 95% CI 0.97–2.82, p=0.06). Polyclonal anti-T cell induction was not associated with lung, kidney, colorectal, or thyroid cancers after transplantation.

Muromonab-CD3

Among VRCs, muromonab-CD3 induction was associated with increased NHL (aIRR=1.37, 95% CI 1.06–1.76, p=0.02) and all VRCs (aIRR 1.29, 95% CI 1.04–1.60, p=0.02) (Table 2). This association with NHL did not change with time from transplant (p-value of interaction=0.3). Muromonab-CD3 induction was not associated with non-NHL VRCs (aIRR=1.02, 95% CI 0.65–1.58, p=0.9), suggesting that its association with all VRCs was driven by its association with NHL. Among non-VRCs, muromonab-CD3 induction was associated with decreased thyroid cancer (aIRR=0.32, 95% CI 0.12–0.80, p=0.01) (Table 3). Muromonab-CD3 induction was not associated with lung, kidney, colorectal cancers, or melanoma after transplantation.

Alemtuzumab

Alemtuzumab induction was also associated with increased NHL (aIRR=1.79, 95% CI 1.02–3.14, p=0.04) and all VRCs (aIRR=1.84, 95% CI 1.11–3.03, p=0.02). The association with NHL did not change with time from transplant (p-value of interaction =0.1). Among non-VRCs, alemtuzumab induction was associated with increased colorectal cancer (aIRR=2.46, 95% CI 1.03–5.91, p=0.04) and thyroid cancer (aIRR=3.37, 95% CI 1.55–7.33, p=0.002). Alemtuzumab induction was not associated with lung, kidney cancer, or melanoma after transplantation.

IL2 Receptor Antagonists

Anti-IL2R induction was not associated with NHL (aIRR=0.82, 95% CI 0.65–1.05, p=0.1), non-NHL VRCs, (aIRR 1.09, 95% CI 0.78–1.51, p=0.6), or all VRCs (aIRR=0.90, 95% CI 0.74–1.10, p=0.3). Among non-VRCs, anti-IL2R induction was associated with decreased lung cancer (aIRR=0.73, 95% CI 0.56–0.95, p=0.02). Anti-IL2R induction was not associated with kidney, colorectal, thyroid cancers, or melanoma after transplantation.

Discussion

In this U.S.-wide study of 111,857 kidney recipients linked to mandatory cancer reporting systems, commonly used antibody induction agents were not associated with increased cancer after kidney transplantation, with the exception of 50% increased melanoma

associated with polyclonal anti-T cell induction. Two infrequently used agents were associated with increased cancer:muromonab-CD3 induction was associated with 37% increased NHL, and alemtuzumab induction was associated with 79% increased NHL, a two and a half fold increase in colorectal cancer, and three fold increase in thyroid cancer after transplantation.

Contrary to some prior studies, (7–11) we found no association between polyclonal anti-T cell induction and NHL or VRCs in kidney recipients. Explanations for this discrepancy include less granular categorizations of induction therapies in previous studies (grouping polyclonal anti-T cell agents with muromonab-CD3) and differing outcomes of interest (PTLD). PTLD is a spectrum of different pathologic diagnoses with different mechanisms of development and risk profiles. NHL is the malignant end of the PTLD spectrum and, after non-melanoma skin cancers, the most common malignancy after transplantation. (19) Poor immune control of EBV has been linked to increased risk for NHL, driving the hypothesis of an association between antibody induction and NHL after transplantation. (18) Previous studies that separated polyclonal anti-T cell induction from muromonab-CD3 were consistent with our findings and did not demonstrate an association between polyclonal anti-T cell induction and NHL after transplantation. (7,16,20,21)

Polyclonal anti-T cell antibody induction was associated with increased melanoma among non-Hispanic white kidney recipients. Most previous reports demonstrate no significant associations between polyclonal anti-T cell induction and grouped non-VRCs, but have not studied melanoma separately. (10,12,22)When we restrict analysis to recipients after 1999 or to those patients that received ATG, this association is of similar magnitude but no longer significant. This could represent decreased power to detect differences and decreased follow-up time. Increased melanoma has been demonstrated in other immunocompromised populations including patients with human immunodeficiency virus (HIV). (3,23) Melanoma is not known to be an infection related cancer. The link between melanoma and polyclonal anti-T cell induction may provide further clues into the relationship between melanoma and the immune system. Screening for melanoma is based on regular skin examinations, which is already part of clinical practice after transplantation due to the elevated risk of non-melanoma skin cancers in this population. (24) More frequent skin examinations may be warranted in those kidney recipients who underwent polyclonal anti-T cell induction.

There has been little controversy concerning the relationship between muromonab-CD3 and NHL after kidney transplantation, and our findings were consistent with previous studies. Those studies with a specific muromonab-CD3 category report risk ratios for NHL after kidney transplantation ranging from 1.72–2.81. (7,9,16) The relationship between muromonab-CD3 and all VRCs appears to be driven by its association with NHL, since we observed no association between muromonab-CD3 and non-NHL VRCs. The association of muronomab-CD3 with NHL is consistent with the perception of increased potency of muromonab-CD3 compared to polyclonal induction agents and has led to decreased use of this agent in recent years.

Previous studies exploring PTLD risk associated with alemtuzumab have been inconclusive. While one study using OPTN data did not find an association between alemtuzumab and

PTLD after kidney transplantation, (11) another using a more recent OPTN cohort did. (16) We found 79% increased NHL associated with alemtuzumab after kidney transplantation. The relationship of alemtuzumab with other cancers has not been previously explored, and a novel finding of our study is the association of alemtuzumab induction with increased colorectal and thyroid cancer in kidney recipients. Neither colorectal cancer nor thyroid cancer has been associated with immunosuppression due to HIV. (25) Of possible relevance, there have been recent findings suggesting a link between colorectal cancer and infection with Fusobacterium species. (26,27) However it is unclear why an infection-related cancer risk would be modestly increased in one set of immunosuppressed patients and not another, and what role alemtuzumab might have in further increasing this risk. With respect to thyroid cancer, in the first set of kidney recipients to receive alemtuzumab, there was a report of autoimmune thyroid disease in one of the nine patients four years after receiving alemtuzumab. (28) Alemtuzumab induction could increase the risk of autoimmune inflammatory processes in the thyroid, in turn increasing risk for thyroid cancer. It is also possible, however, that the increased detection of thyroid cancers in this population could be an artifact of increased screening in this context. (29) Alternatively, there may be intrinsic oncogenic properties of alemtuzumab that have not been noted.

Our study addresses some of the major limitations of prior post-transplant cancer studies, including sample size, lack of long-term follow-up, and incomplete ascertainment of cancer outcomes. Because of increased sample size, we were able to test associations between more clinically and mechanistically homogenous categorizations of induction agents (including alemtuzumab) than previous reports. We were also able to analyze associations with several individual cancers with increased incidence following transplantation. Our findings for grouped VRCs should be considered with caution, because these cancer types differ in their etiology and it is possible that induction agents affect immune control of each virus in diverse ways.

There are a number of important limitations of our study to consider. There is a possibility of underreporting of both incident cancer and induction medication. The cancer registries used are population based registries with mandatory reporting of all incident cancers, but it is possible that transplant recipients may have moved away from states with mandatory reporting or linkage. In previous analysis, the rate of emigration is estimated to be 5.8% at 10 years after transplant. (2) The duration of follow-up was limited for some transplant recipients, which affected our ability to look at associations of induction with long-term cancer risk. There could also be underreporting or misclassification of induction medications in the SRTR. We were not able to control for dose and administration schedule of induction medications or subsequent treatment with the same medications for rejection. Because of difference in rejection rates by immunosuppression protocols, and subsequent need for additional immunosuppression based on rejection rates, an intention-to-treat design was chosen. In other words, patients who received antibody agents for subsequent rejection episodes were classified by their original induction protocol. It is important to note that the cancer registries used do not capture non-melanoma skin cancers and we were unable to make any conclusions on these cancers despite the high risk and incidence of these cancers after transplantation. Finally, we make a number of comparisons throughout this study.

Given these multiple comparisons, there is a risk of alpha inflation, that is detecting significant relationships where they do not exist.

We have shown in a large, population-based cohort of kidney recipients, that there is little evidence to support the concern for increased cancer risk with the most commonly used induction agents. Increased NHL was seen with muromonab-CD3, an agent that has generally been supplanted by polyclonal anti-T cell induction, and alemtuzumab, which remains in extremely limited use. Our findings highlight the need for continued surveillance of alemtuzumab and further research into the mechanisms for the increased risk across a diverse group of cancers after transplantation. Commonly used induction agents, including the most modern polyclonal anti-T cell and anti-IL2R agents, are largely safe with regard to cancer risk after transplantation. There might be a role for increased melanoma screening for those patients treated with polyclonal anti-T cell induction, although absolute risk for this malignancy remains relatively low. Treatment decisions regarding the use of these agents should focus more on the balance between rejection prevention and acute infection rather than the risk of malignancy.

Materials and Methods

Transplant Cancer Match Study

The TCM Study (http://transplantmatch.cancer.gov/) links transplant records from the SRTR to 15 state and regional population-based U.S. cancer registries with mandatory reporting of all cancers except basal cell and squamous cell skin cancer. Currently the TCM Study includes 43% of the U.S. transplant population between 1987 and 2009. The study was approved by human subjects committees at the National Cancer Institute and, as required, at participating cancer registries.

Study Population and Exposure Definition

Kidney recipients transplanted between 1987 and 2009 in the TCM Study, with cancer registry coverage at the time of transplant, were included. When listing immunosuppression, centers specify if each agent was used for induction, maintenance, or rejection treatment; an agent was considered "induction" if the purpose was listed as induction and if usage occurred during the initial transplant hospitalization. Those recipients listed as having received more than one induction agent were excluded (~2%). Antibody induction agents were classified as polyclonal anti-T cell (anti-lymphocyte globulin, equine anti-thymocyte globulin, and rabbit anti-thymocyte globulin), muromonab-CD3 (monoclonal anti-T cell), alemtuzumab (anti-CD52), or anti-IL2R (IL-2 receptor inhibitors daclizumab and basiliximab). Patients who received antibody agents for subsequent rejection episodes were classified by their original induction protocol.

Cancer Outcomes

Cancers in kidney recipients were identified through linked records in participating cancer registries. Recipients were considered at risk from transplantation until the earliest of graft failure, retransplantation, death, loss to follow-up, or end of cancer registry coverage. The outcomes of interest were specific cancers that are common and occur with increased

incidence after transplantation: NHL and cancers of the lung, colorectum, kidney, and thyroid among the entire study population, and melanoma among non-Hispanic white recipients. Among transplant recipients, most NHLs are caused by Epstein-Barr virus (EBV). (18) We grouped together other virus-related cancers (VRCs) including Hodgkin lymphoma (EBV), cancers of the cervix, vagina, vulva, anus, penis, oropharynx, and tonsil (human papillomavirus), Kaposi sarcoma (human herpes virus 8), and liver cancer (hepatitis B, hepatitis C) for a composite outcome because they were too uncommon to examine separately.

Statistical Analysis

Multivariable Poisson regression models were used to quantify the risk of incident cancers associated with induction therapy. In each model, we compared risk in transplants treated with one type of antibody induction with transplants not treated with any induction. Models were adjusted for age at transplantation, gender, race, retransplantation, zero HLA mismatch status, receipt of a living donor kidney and year of transplantation. It has been demonstrated that there are different risk factors for early vs. late NHL and it might be expected that antibody immunosuppression would especially increase risk early after transplantation. (15) We assessed whether the effect of antibody induction on NHL risk differed early (2 years) and late after transplantation (>2 years) using an interaction term between the induction category and a time-varying marker for the first two years after transplantation. The use of antibody induction agents has changed over time. To take this into account, analyses for each category of induction immunosuppression were limited to those years for which at least 20 recipients in the United States received that agent (polyclonal: 1987–2009; muromonab-CD3: 1988–2003; alemtuzumab: 2001–2009; anti-IL2R: 1995–2009). Within the polyclonal anti-T cell induction category, induction with rabbit anti-thymocyte globulin (in particular ATG), has predominated since it gained U.S. Food and Drug Administration (FDA) approval in 1998; interestingly, FDA approval was given for treatment of rejection, and the highly prevalent use for induction is off-label. As additional sensitivity analyses, we looked only at those kidney recipients who received polyclonal anti-T induction after 1999 and only those kidney recipients who received ATG. All analyses were performed using Stata 11.0/MP for Linux (StataCorp, College Station, TX, www.stata.com).

Acknowledgments

The authors gratefully acknowledge the support and assistance provided by individuals at the Health Resources and Services Administration (including Monica Lin), the SRTR (Ajay Israni, Bertram Kasiske, Paul Newkirk, Jon Snyder), and the following cancer registries: the states of California (Christina Clarke), Colorado (Jack Finch), Connecticut (Lou Gonsalves), Florida (Brad Wohler), Georgia (Rana Bayakly), Hawaii (Marc Goodman), Iowa (Charles Lynch), Illinois (Lori Koch), Michigan (Glenn Copeland), New Jersey (Karen Pawlish, Xiaoling Niu), New York (Amy Kahn), North Carolina (Chandrika Rao), Texas (Melanie Williams), and Utah (Janna Harrell), and the Seattle-Puget Sound area of Washington (Margaret Madeleine). We also thank analysts at Information Management Services for programming support (David Castenson, Ruth Parsons).

The views expressed in this paper are those of the authors and should not be interpreted to reflect the views or policies of the National Cancer Institute, Health Resources and Services Administration, SRTR, cancer registries, or their contractors.

During the initial period when registry linkages were performed, the SRTR was managed by Arbor Research Collaborative for Health in Ann Arbor, MI (contract HHSH234200537009C); beginning in September 2010, the SRTR was managed by Minneapolis Medical Research Foundation in Minneapolis, MN (HHSH250201000018C).

The following cancer registries were supported by the National Program of Cancer Registries of the Centers for Disease Control and Prevention: California (agreement 1U58 DP000807-01), Colorado (U58 DP000848-04), Georgia (5U58DP000817-05), Illinois (5658DP000805-04), Michigan (5U58DP000812-03), New Jersey (5U58/DP000808-05), New York (15-0351), North Carolina (U58DP000832), and Texas (5U58DP000824-04). The following cancer registries were supported by the SEER Program of the National Cancer Institute: California (contracts HHSN261201000036C, HHSN261201000035C, and HHSN261201000034C), Connecticut (HHSN261201000024C), Hawaii (HHSN261201000037C, N01-PC-35137, and N01-PC-35139), Iowa (N01-PC-35143), New Jersey (HHSN261201000027C N01-PC-54405), Seattle-Puget Sound (N01-PC-35142), and Utah (HHSN261201000026C). Additional support was provided by the states of California, Colorado, Connecticut, Illinois, Iowa, New Jersey, New York (Cancer Surveillance Improvement Initiative 14-2491), Texas, and Washington, as well as the Fred Hutchinson Cancer Research Center in Seattle, WA.

Abbreviations

aIRR adjusted incidence rate ratios

NHL non-Hodgkin lymphoma

PTLD post-transplant lymphoproliferative disorder

OPTN Organ Procurement and Transplantation Network

SRTR Scientific Registry of Transplant Recipients

TCM Transplant Cancer Match

ALG anti-lymphocyte globulin

ATGAM equine anti-thymocyte globulin

ATG rabbit anti-thymocyte globulin

EBV Epstein Barr virus

VRC virus related cancers

FDA U.S. Food and Drug Administration

HIV human immunodeficiency virus

References

- 2008 Annual Report of the US Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1998–2007.
- 2. Engels EA, Pfeiffer RM, Fraumeni JF Jr, Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011 Nov 2; 306(17):1891–1901. [PubMed: 22045767]
- Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/ AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet. 2007 Jul 7; 370(9581):59–67. [PubMed: 17617273]
- 4. Kiberd BA, Rose C, Gill JS. Cancer mortality in kidney transplantation. Am J Transplant. 2009 Aug; 9(8):1868–1875. [PubMed: 19563337]
- Brennan DC, Daller JA, Lake KD, Cibrik D, Del Castillo D, Thymoglobulin Induction Study Group. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. N Engl J Med. 2006 Nov 9; 355(19):1967–1977. [PubMed: 17093248]
- Hanaway MJ, Woodle ES, Mulgaonkar S, Peddi VR, Kaufman DB, First MR, et al. Alemtuzumab induction in renal transplantation. N Engl J Med. 2011 May 19; 364(20):1909–1919. [PubMed: 21591943]

7. Caillard S, Dharnidharka V, Agodoa L, Bohen E, Abbott K. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation. 2005 Nov 15; 80(9):1233–1243. [PubMed: 16314791]

- 8. Hibberd AD, Trevillian PR, Wlodarzcyk JH, Gillies AH, Stein AM, Sheil AG, et al. Cancer risk associated with ATG/OKT3 in renal transplantation. Transplant Proc. 1999 Feb-Mar;31(1–2):1271–1272. [PubMed: 10083567]
- van Leeuwen MT, Grulich AE, Webster AC, McCredie MR, Stewart JH, McDonald SP, et al. Immunosuppression and other risk factors for early and late non-Hodgkin lymphoma after kidney transplantation. Blood. 2009 Jul 16; 114(3):630–637. [PubMed: 19443660]
- Bustami RT, Ojo AO, Wolfe RA, Merion RM, Bennett WM, McDiarmid SV, et al. Immunosuppression and the risk of post-transplant malignancy among cadaveric first kidney transplant recipients. Am J Transplant. 2004 Jan; 4(1):87–93. [PubMed: 14678038]
- 11. Kirk AD, Cherikh WS, Ring M, Burke G, Kaufman D, Knechtle SJ, et al. Dissociation of depletional induction and posttransplant lymphoproliferative disease in kidney recipients treated with alemtuzumab. Am J Transplant. 2007 Nov; 7(11):2619–2625. [PubMed: 17868060]
- Pedotti P, Cardillo M, Rossini G, Arcuri V, Boschiero L, Caldara R, et al. Incidence of cancer after kidney transplant: results from the North Italy transplant program. Transplantation. 2003 Nov 27; 76(10):1448–1451. [PubMed: 14657684]
- 13. Marks WH, Ilsley JN, Dharnidharka VR. Posttransplantation lymphoproliferative disorder in kidney and heart transplant recipients receiving thymoglobulin: a systematic review. Transplant Proc. 2011 Jun; 43(5):1395–1404. [PubMed: 21693205]
- Cherikh WS, Kauffman HM, McBride MA, Maghirang J, Swinnen LJ, Hanto DW. Association of the type of induction immunosuppression with posttransplant lymphoproliferative disorder, graft survival, and patient survival after primary kidney transplantation. Transplantation. 2003 Nov 15; 76(9):1289–1293. [PubMed: 14627905]
- 15. Quinlan SC, Pfeiffer RM, Morton LM, Engels EA. Risk factors for early-onset and late-onset post-transplant lymphoproliferative disorder in kidney recipients in the United States. Am J Hematol. 2011 Feb; 86(2):206–209. [PubMed: 21264909]
- 16. Dharnidharka VR, Lamb KE, Gregg JA, Meier-Kriesche HU. Associations Between EBV Serostatus and Organ Transplant Type in PTLD Risk: An Analysis of the SRTR National Registry Data in the United States. Am J Transplant. 2012 Jan 6.
- 17. Kasiske BL, Kukla A, Thomas D, Wood Ives J, Snyder JJ, Qiu Y, et al. Lymphoproliferative disorders after adult kidney transplant: epidemiology and comparison of registry report with claims-based diagnoses. Am J Kidney Dis. 2011 Dec; 58(6):971–980. [PubMed: 21930332]
- Opelz G, Daniel V, Naujokat C, Dohler B. Epidemiology of pretransplant EBV and CMV serostatus in relation to posttransplant non-Hodgkin lymphoma. Transplantation. 2009 Oct 27; 88(8):962–967. [PubMed: 19855238]
- Harris NL, Ferry JA, Swerdlow SH. Posttransplant lymphoproliferative disorders: summary of Society for Hematopathology Workshop. Semin Diagn Pathol. 1997 Feb; 14(1):8–14. [PubMed: 9044505]
- 20. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant. 2004 Feb; 4(2):222–230. [PubMed: 14974943]
- Dharnidharka VR, Stevens G. Risk for post-transplant lymphoproliferative disorder after polyclonal antibody induction in kidney transplantation. Pediatr Transplant. 2005 Oct; 9(5):622– 626. [PubMed: 16176420]
- 22. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. Am J Transplant. 2004 Jun; 4(6):905–913. [PubMed: 15147424]
- 23. Lanoy E, Dores GM, Madeleine MM, Toro JR, Fraumeni JF Jr, Engels EA. Epidemiology of nonkeratinocytic skin cancers among persons with AIDS in the United States. AIDS. 2009 Jan 28; 23(3):385–393. [PubMed: 19114864]
- 24. Chapman JR. The KDIGO clinical practice guidelines for the care of kidney transplant recipients. Transplantation. 2010 Mar 27; 89(6):644–645. [PubMed: 20164816]

25. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet. 2007 Jul 7; 370(9581):59–67. [PubMed: 17617273]

- 26. Castellarin M, Warren RL, Freeman JD, Dreolini L, Krzywinski M, Strauss J, et al. Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. Genome Res. 2011 Oct 18.
- 27. Kostic AD, Gevers D, Pedamallu CS, Michaud M, Duke F, Earl AM, et al. Genomic analysis identifies association of Fusobacterium with colorectal carcinoma. Genome Res. 2011 Oct 18.
- 28. Kirk AD, Hale DA, Swanson SJ, Mannon RB. Autoimmune thyroid disease after renal transplantation using depletional induction with alemtuzumab. Am J Transplant. 2006 May; 6(5 Pt 1):1084–1085. [PubMed: 16611348]
- Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002.
 JAMA. 2006 May 10; 295(18):2164–2167. [PubMed: 16684987]

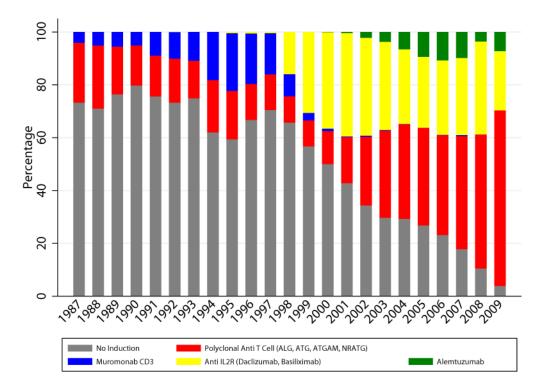


Figure 1. Use of induction immunosuppression in kidney transplant recipients in the United States, 1987–2009.

Author Manuscript

Table 1

Kidney recipients in the United States, by induction immunosuppression, 1987-2009.

	No Induction	No Induction Polyclonal Anti-T Cell Muromonab-CD3 Alemtuzumab	Muromonab-CD3	Alemtuzumab	Anti-IL2R
	N=51,954	N=27,117	N=6,218	N=3,394	N=23,173
Age at transplantation in years, Mean(SD)	43 (15)	46 (15)	41 (14)	48 (14)	45 (17)
Male	30,962 (59.6)	15,681 (57.8)	3,644 (58.6)	1,957 (57.7)	14,259 (61.5)
Racea					
White	29,379 (56.9)	14,252 (53.0)	3,344 (54.1)	1,733 (51.5)	11,593 (50.4)
Black	10,035 (19.4)	7,059 (26.2)	1,525 (24.7)	797 (23.7)	4,680 (20.3)
Hispanic/Other	12,238 (23.7)	5,606 (20.8)	1,315 (21.3)	835 (24.8)	6,741 (29.3)
Retransplants	3,517 (6.8)	3,848 (14.2)	630 (10.1)	403 (11.9)	1,931 (8.3)
Zero HLA Mismatch	7,220 (14.1)	3,141 (11.7)	562 (9.1)	429 (12.7)	2,951 (12.8)
Living Donor	20,540 (39.5)	7,874 (29.0)	1,013 (16.3)	1,597 (47.0)	9,647 (41.6)

All cells display N (%) except age at transplantation. Polyclonal Anti-T Cell = anti-lymphocyte globulin (ALG), equine anti-thymocyte globulin (ATGAM), and rabbit anti-thymocyte globulin (NRATG, NRATS, and ATG); Anti-IL2R = daclizumab and basiliximab

 $^{^{\}it d}$ Numbers do not sum to total due to missing data.

Hall et al.

Table 2

Association between induction therapy and incident virus-related cancers.

Page 14

	C N	-	IDD (050/ CI)	D 77 1
	Cancers, N	Incidence ^a	aIRR (95% CI)	P-Value
NHL				
No Induction	377	142.1	Reference	
Polyclonal	125	131.6	0.96 (0.77-1.20)	0.7
Muromonab-CD3	80	210.9	1.37 (1.06–1.76)	0.02
Alemtuzumab	15	216.2	1.79 (1.02–3.14)	0.04
Anti-IL2R	96	114.9	0.82 (0.65-1.05)	0.1
Non-NHL VRCs				
No Induction	164	61.8	Reference	
Polyclonal	56	60.0	1.11 (0.82–1.53)	0.5
Muromonab-CD3	25	65.9	1.02 (0.65–1.58)	0.9
Alemtuzumab	4	57.6	2.05 (0.66-6.33)	0.2
Anti-IL2R	53	63.5	1.09 (0.78–1.51)	0.6
All VRCs				
No Induction	541	203.9	Reference	
Polyclonal	181	190.6	1.01 (0.84–1.21)	0.9
Muromonab-CD3	104	276.8	1.26 (1.01–1.57)	0.04
Alemtuzumab	19	273.8	1.84 (1.11–3.03)	0.02
Anti-IL2R	149	178.4	0.90 (0.74-1.10)	0.3

a per 100,000 person-years

Adjusted incidence rate ratios for virus-related cancers after kidney transplantation. The number of cancers diagnosed in each stratum is shown (N). Virus-related cancers (VRCs) included non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, HPV-related cancers (cancers of the cervix, vagina, vulva, anus, penis, oropharynx, and tonsil), Kaposi sarcoma, and liver cancer. All models were adjusted for recipient age, gender, race, retransplantation, zero HLA mismatch status, receipt of living donor kidney and year of transplant. Only transplants completed in years with at least 20 recipients receiving the induction therapy of interest were included: polyclonal 1987–2009, muromonab-CD3 1987–2003, alemtuzumab 2001–2009, anti-IL2R 1995–2009.

Polyclonal anti-T cell = anti-lymphocyte globulin (ALG), equine anti-thymocyte globulin (ATGAM), and rabbit anti-thymocyte globulin (NRATG, NRATS, and ATG); Anti-IL2R = daclizumab and basiliximab; aIRR = adjusted incidence rate ratio; NHL = non-Hodgkin lymphoma; VRCs = non-Hodgkin lymphoma, Hodgkin lymphoma, HPV-related cancers (cancers of the cervix, vagina, vulva, anus, penis, oropharynx, and tonsil), Kaposi sarcoma, and liver cancer

Hall et al.

Page 15

 Table 3

 Association between induction therapy and incident non-virus-related cancers.

	Cancers, N	Incidence ^a	aIRR (95% CI)	P-Value
Lung Cancer				
No Induction	297	111.9	Reference	
Polyclonal	127	133.7	1.14 (0.91–1.43)	0.2
Muromonab-CD3	46	121.3	1.03 (0.75–1.41)	0.8
Alemtuzumab	7	100.9	0.93 (0.42-2.07)	0.9
Anti-IL2R	77	92.2	0.73 (0.56-0.95)	0.02
Kidney Cancer				
No Induction	261	98.4	Reference	
Polyclonal	121	127.4	1.08 (0.85-1.38)	0.5
Muromonab-CD3	34	89.6	0.93 (0.65-1.34)	0.7
Alemtuzumab	11	158.5	1.20 (0.63-2.30)	0.6
Anti-IL2R	102	122.1	1.03 (0.81-1.32)	0.8
Colorectal Cancer				
No Induction	164	61.8	Reference	
Polyclonal	60	63.2	1.14 (0.82–1.58)	0.4
Muromonab-CD3	20	52.7	0.77 (0.48–1.24)	0.3
Alemtuzumab	7	100.9	2.46 (1.03-5.91)	0.04
Anti-IL2R	47	56.3	0.88 (0.62-1.25)	0.5
Thyroid Cancer				
No Induction	103	38.8	Reference	
Polyclonal	26	27.4	0.65 (0.40-1.04)	0.07
Muromonab-CD3	5	131.8	0.32 (0.12-0.80)	0.01
Alemtuzumab	10	144.1	3.37 (1.55–7.33)	0.002
Anti-IL2R	27	32.3	0.81 (0.51-1.29)	0.4
$Melanoma^b$				
No Induction	107	68.7	Reference	
Polyclonal	56	103.4	1.50 (1.06–2.14)	0.02
Muromonab-CD3	11	51.1	0.77 (0.41–1.45)	0.4
Alemtuzumab	3	81.1	1.14 (0.33–3.95)	0.8
Anti-IL2R	38	88.1	1.15 (0.77–1.72)	0.5

a per 100,000 person-years

Adjusted incidence rate ratios for non-virus-related cancers (non-VRC) after kidney transplantation. The number of cancers diagnosed in each stratum is shown (N). All models were adjusted for recipient age, gender, race, retransplantation, zero HLA mismatch status, receipt of living donor kidney and year of transplant. Only transplants completed in years with at least 20 recipients receiving the induction therapy of interest were included: polyclonal 1987–2009, muromonab-CD3 1987–2003, alemtuzumab 2001–2009, anti-IL2R 1995–2009.

Polyclonal anti-T cell = anti-lymphocyte globulin (ALG), equine anti-thymocyte globulin (ATGAM), and rabbit anti-thymocyte globulin (NRATG, NRATS, and ATG); Anti-IL2R = daclizumab and basiliximab; aIRR = adjusted incidence rate ratio

b among non-Hispanic white kidney recipients